Research Article [Sarode et al., 5(8): Aug., 2014:3787-3798]
CODEN (USA): IJPLCP ISSN: 0976-7126

INTERNATIONAL JOURNAL OF PHARMACY & LIFE SCIENCES
(Int. J. of Pharm. Life Sci.)

Preparation and Characterization of Sustained release Antidepressant tablet using combination of wax

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Abstract

Developing oral controlled release tablets for highly water soluble drugs with constant release rate has always been a challenge to the pharmaceutical technologist. Most of these highly water soluble drugs if not formulated properly, may readily release the drugs at faster rate, and are likely to produce the toxic concentrations of the drug on oral administration. Various waxes such as fatty acids, fatty alcohols, natural waxes and glycerides have been used, that melts at relatively low temperature and solidifies at room temperature to form solid dosage forms for decades. Drug release is decreased from the matrix with the increased molecular weight of the wax. When single wax is used as a binder, for sustained release, the concentration of wax needed is higher for obtaining required drug release profile. Venlafaxine Hydrochloride is a novel antidepressant which is highly water soluble. It is unique antidepressant that differs structurally from other currently available antidepressants. Venlafaxine and its active metabolite, O-desethyl venlafaxine (ODV), inhibits the neuronal uptake of norepinephrine, serotonin and to a lesser extent dopamine but have no monoamine oxidase inhibitory activity and low affinity for brain muscarnic, cholinergic, histaminergic or alpha-adrenergic receptors. Hence it lacks the adverse cholinergic, sedative and cardiovascular effects of tricyclic antidepressants. Melt granulation was used as method of preparation. It is advantageous compared with an ordinary wet granulation process, since the liquid addition phase as well as drying phase of the process is eliminated. it can be concluded that sustained release wax matrix tablets were prepared successfully using the combination of carnauba wax and Hydrogenated castor oil for a highly water soluble drug, Venlafaxine Hydrochloride.

Key-Words: Antidepressant, Wax, Tablet

Introduction

Developing oral controlled release tablets for highly water soluble drugs with constant release rate has always been a challenge to the pharmaceutical technologist. Most of these highly water soluble drugs if not formulated properly, may readily release the drugs at faster rate, and are likely to produce the toxic concentrations of the drug on oral administration.

Various waxes such as fatty acids, fatty alcohols, natural waxes and glycerides have been used, that melts at relatively low temperature and solidifies at room temperature to form solid dosage forms for decades. Drug release is decreased from the matrix with the increased molecular weight of the wax. When single wax is used as a binder, for sustained release, the concentration of wax needed is higher for obtaining required drug release profile.

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History

The history of controlled release technology can be divided roughly in to three time periods.

1950-1970:- It is a period of sustained drug release. A number of systems containing hydrophobic polymers and waxes were fabricated with drugs into dosage forms with the aim of sustaining drug levels and hence drug action for an extended period of time. However, a lack of understandings of anatomical and physiological barriers imposed impediments on the development of efficient delivery systems.

1970-1990:- It was involved in the determination of the needs in controlled drug delivery and to understand the barriers of various routes of administration.

Post 1990:- It is the modern era of controlled release technology and represents the period in which an attempt at drug optimization is emphasized.

Controlled drug delivery occurs when a polymer whether natural or synthetic, is judiciously combined

with a drug or other active agent in such a way that the active agent is released from the material in a predesigned manner. The release of active agent may be constant over a long period, or it may be triggered by the environment or other external events.

The potential benefits that a controlled-release drug delivery system may bring to us can be appreciated by a consideration of prolonged and efficient delivery of therapeutically effective dosages, patient compliance and localization of therapy. Optimal therapy of a disease requires the efficient delivery of active drugs to the tissues or organs that need treatment. Pharmacological activity and therapeutic efficacy are known to depend up on the concentration of drug reaching the ailing tissue cells. It is usually desirable, from the standpoint of pharmacodyanamics, to maintain the drug concentration in the ailing tissue cells at a constant level and within a therapeutically effective dose range for as long as the treatment requires. Very often, doses far in excess of those required in the cells have to be administered in order to achieve the necessary therapeutically effective concentration. Unfortunately, this massive dosing frequently leads to resistance and elicit undesirable immunological and toxicological effects in non target tissues. The bioavailability to a target tissue can be maximized and the adverse side effects in the nontarget tissue can be minimized by applying the principles of controlled drug administration.[1,2]

Administration of drugs in conventional dosage forms often results in seesaw fluctuations of drug concentrations in systemic circulation and tissue compartments. A well designed, controlled release drug delivery system can significantly reduce the frequency of drug dosing and also maintain steady drug concentration in blood circulation and target tissue cells. The prolonged release characteristics of the controlled release drug delivery systems minimize the need for frequent drug intake and thus assures better compliance with the prescribed medication regimen. Drug concentrations can be maintained within a narrow therapeutic range by the use of controlled release drug delivery systems which will also minimize the incidence and severity of adverse side effects.[3]

Methods used to achieve sustained release

For controlled release systems, the oral route of administration has, by far, received the most attention. The more common methods used to achieve sustained release for orally administered drugs are Diffusion Systems, Dissolution Systems, Osmotic System, Ion-Exchange resins.

Diffusion Systems

In these systems, the release rate of drug is determined by its diffusion through a water insoluble polymer. There are basically two types of diffusion devices:

- Reservoir devices
- Matrix devices

Reservoir Devices: This is a device in which core of drug is surrounded by a polymeric membrane. The release of drug from a reservoir device is governed by Fick's first law of diffusion common methods used to develop reservoir type devices include microencapsulation of drug particles and press-coating of tablets containing drug cores.

Matrix Devices: These are devices in which dissolved or dispersed drug is distributed uniformly in an inert polymeric matrix. The rate of release of drug dispersed as a solid in an inert matrix has been described by Higuchi.

In these devices it is assumed that solid drug dissolves from surface layer of device first, when this layer becomes exhausted of drug, the next layer begins to be depleted by dissolution and diffusion through the matrix to the external solution. In this fashion, the interface between the region containing dissolved drug and that containing dispersed drug moves into the interior as a front. The three major types of materials used in the preparation of matrix devices are insoluble plastics, hydrophilic polymers and fatty compounds.[2,3]

Materials used as Retardants in Matrix Tablet Formulations

Matrix Characteristics	Material
Insoluble, inert	Polyethylene, Polyvinyl chloride, Methyl acrylate methacry late copolymer, Ethyl cellulose
Insoluble, erodable	Carnauba wax, Stearyl alcohol, Stearicacid polyethyleneglycol Triglycerides.
Hydrophilic	Methyl cellulose (400cps, 4000cps,), Hydroxyethyl cellulose, Hydroxypropylmethyl cellulose, Sodium carboxy methyl cellulose, Carboxypoly methylene, Galactomannose, Sodium alginate.

Classification of Matrix Systems [25,22,21]

Matrix System can be based on several criteria, namely

- Matrix Structure
- Release Kinetics
- Controlled release properties
- Chemical nature and properties of applied materials

Classification of Matrix System based on chemical nature and properties of the matrix system

Mineral matrices	Hydrophilic Matrices	Inert Matrices	Lipid Matrices	Biodegradable Matrices
Drug retained in support	Unlimited swelling	Controlled delivery by diffusion	Delivery by diffusion	non lipid
Drug absorbed on support	Limited swelling and controlled delivery through swelling			

Dissolution Systems

A drug with a slow dissolution rate will yield an inherently sustained blood level. In principle, then, it would seem possible to prepare controlled release products by controlling the dissolution rate of drugs that are highly water soluble. This can be done by preparing an appropriate salt or derivative, by coating the drug with a slowly soluble material, or by incorporation it into a tablet with a slowly soluble carrier. Ideally surface area available for dissolution must remain constant to achieve a constant release rate. Most of the products fall in to two categories encapsulated dissolution systems and matrix dissolution systems.

Encapsulated dissolution systems can be prepared either by coating particles or granules of drug with varying thickness of slowly soluble polymers or by micro encapsulation. The coating materials used are gelatin, carnauba wax, shellacs, ethyl cellulose, cellulose acetate phthalate or cellulose acetate butyrate. Matrix dissolution devices are prepared by compressing the drug with a slowly soluble polymer carrier into a tablet form.

Osmotic Systems, Ion-exchange resins, swelling and expanding systems, Floating systems and Bioadhesive systems are other controlled. Release drug delivery systems.[4,5]

Waxes [9,24,26]

Wax is chemically defined as an ester of a monohydric long chain fatty alcohol and long chain fatty acid. Generally wax refers to a substance which is plastic solid at room temperature and liquid of low viscosity above its melting point. Waxes usually contain a wide variety of materials including glycerides, fatty alcohols and fatty acids and their esters. In pharmaceutical literature, the terms waxes, fats or lipids have often been used interchangeably.

Waxes have in common their lipophilic character, insolubility in water and solubility in nonpolar solvents. Besides natural materials, many semi synthetic products such as fatty acids or alcohols or surfactants are derived from lipids. Waxes have been used in pharmaceutical industry for many years. Their applications in semisolid preparations including ointments, creams or lotions and suppositories are well known.

Because of their lipophilic properties, waxes are used in sustained release single or multiple unit solid dosage forms.

Classification of Waxes[10]

Based on various sources, Waxes are classified into

Animal Waxes: Lanolin is an animal wax obtained from the wool of sheep. spermaceti wax is obtained by precipitation of head oil from the sperm whale up on cooling. It primarily consists of cetylpalmitate.

Insect Waxes: Bees wax is commonly used insect wax obtained from honey comb of the bee. White Beeswax is obtained by bleaching yellow Beeswax with oxidizing agents or sunlight.

Plant waxes: Carnauba wax is plant derived and obtained from the carnauba palm tree, indigenous to Brazil. Wax is obtained from the surface of dried leaves.

Vegetable and Synthetic Waxes: Hydrogenated vegetable oils are prepared hydrogenation of refined vegetable oils.

It's of 2 types.

Type - I : Melts in the range of 57-70^{o}C and has Iodine value of 0-5.

Type - II: Partially hydrogenated vegetable oils and has a lower melting range and a higher Iodine value than type - I.

Hydrogenated cottonseed oil, Hydrogenated castor oil, Hydrogenated palm oil are some examples.

Mineral Waxes: These are waxes with high viscosity and high melting point. Examples of these waxes are microcrystalline wax and petroleum wax.

Classification of waxes

S/No.	Source	Example
1	Animal	Lanolin, Spermaceti
2	Insect	Bees wax
3	Vegetable/Synthetic	Hydrogenated Cotton Seed Oil (Lubritab)
		Hydrogenated Palmoil (Dynasan P60)
		Hydrogenated Soyabean oil (Softisan

		154)
4	Plantwax	Carnaubawax
5	Mineral Wax	Petroleum wax, Micro crystalline wax

Characterization

Harvesting of animal, plant or insect waxes is often from wild, non-cultivated sources and because of their complex composition, it is important to characterize their physical and chemical properties.

The composition of natural materials often varies with location, whether, season of harvesting and age. A good quality control of raw materials is of utmost importance in order to obtain pharmaceutical products of high quality.

Chemical

Saponification value: It is defined as number of milligrams of potassium hydroxide (KOH) required neutralizing the free fatty acid obtained by complete hydrolysis of one gram of wax, oil or fat. It indicates the average molecular weight.

Acid Value: It is defined as the number of milligrams of potassium hydroxide (KOH) required neutralizing the free fatty acid in one gram of the sample. It indicates a proportion of free fatty acid in their composition.

Ester Value: It indicates the amount of ester present. It is obtained by subtracting the acid value a from the saponification value.

Iodine Value: It measures the number of unsaturated bonds equivalent to iodine molecule. It is defined as grams of iodine absorbed by 100 grams of oils and fats.

Peroxide Value: Indicates the extent of oxidation of waxes or fats. Waxes with high peroxide value are more liable to rancidity.

Physical

Melting Point: Wax is non homogenous in composition so melting point range is obtained rather than clear melting point. Melting point of waxes is determined by capillary tube. Melting point depends on (a) Hydroxyl number (b) Degree of unsaturation (c) Molecular weight.

Slip Point: It is defined as temperature at which a column of testing material starts raising in an open ended capillary tube, which in clipped in a water-filled beaker and heated under specific conditions.

Congealing Point: It is the temperature at which molten wax stops to flow upon cooling.

Heating and cooling profiles of wax: Expansion and contraction of waxes is important in the processing of wax melts.

Heating and cooling profiles of waxes can be characterized by differential scanning calorimetry (DSC) in a qualitative and quantitative manner. The dilation of waxes or thermal expansion during the transition from the solid to the liquid state can be measured with dilatometer.

Molecular Weight: Molecular weight is an important parameter which provides the valuable information about refractive index, strength and rheological behavior of waxes and fats predominantly contain triglycerides. Besides triglycerides, waxes also contain some complex mixture of high molecular weight organic compounds in minor quantities. As molecular weight of fats and waxes increase the ability of waxes to retard the drug release from dosage form increases.

Viscosity: The viscosity of a molten wax is an important parameter for the processes such as hot melt coating and spray congealing.

The time which a certain quantity of molten wax requires to flow through an orifice of specified dimension is measured in ASTM D-88.

Venlafaxine Hcl is well absorbed and extensively metabolized in liver O-desmethyl venlafaxine (ODV) is the only major active metabolite. On the basis of the mass balance studies, at least 92% of single oral dose of venlafaxine HCl is absorbed. The absolute bioavailability is about 45%. The apparent elimination half life is 5±2 and apparent (steady-state) volume of distribution is 7.5± 3.7 L/Kg. It belongs to BCS class I (highly soluble, highly permeable) drug. Venlafaxine Hydrochloride has been used as model drug in this studies.

In forming wax matrix system, different methods such as dry blending, wet granulation, melt granulation and extrusion spheronization have been used with various waxes.

Melt granulation is the method of preparation used in this study. Melt granulation is also called as thermoplastic granulation. It is the process in which granulation is obtained through the addition of a binder which melts or softens at a relatively low temperature. After melting, the binder acts like a binding liquid.

Melt granulation is advantageous compared with an ordinary wet granulation process. Since the liquid addition phase of the process is eliminated. Consequently melt granulation requires less heat energy. Melt granulation is an alternative to the use of solvents when granulating water sensitive materials.

The objectives of present investigation are

To prepare a sustained release matrix tablet using the combination of two waxes and to evaluate various physico-chemical parameters and in-vitro release of venlafaxine Hydrochloride.

To evaluate the effect of various processing parameters and formulation parameters on *invitro* drug release.
To evaluate the effect of the heat treatment on wax matrix formulation and subsequent drug release.

Material and Methods

Venlafaxine Hydrochloride was obtained as gift sample from Alembic limited, Vadodara,
Carnauba wax & Hydrogenated Castor oil were obtained as gift sample from Jayant Agro Organics Limited, Mumbai, the other chemicals ; Microcrystalline Cellulose ; Dicalcium Phosphate dihydrate DCPD; Corn Starch; Magnesium Stearate were purchased from S.D. Fine Chemicals, Mumbai.

Formulation of Wax Matrix Tablets [7,8]

The formulation was based on 37.5mg dose of venlafaxine Hydrochloride as a model drug and tablet weight was set at 250 mg. The batch size was 25 grams. Tablets contained 25% of carnauba wax, 15% of Hydrogenated Castor oil, 15% Venflaxine Hydrochloride, 43% of Dicalcium Phosphate dihydrate. (DCPD), 1% of Magnesium stearate, 1% of talc.

Methods of preparation

- Melt Granulation
- Partial Melt granulation
- Wet Granulation
- Direct Compression

Melt Granulation or Thermoplastic granulation

Hydrogenated castor oil wax flakes were melted at first in a heating mantel then carnauba wax flakes were added. In the molten waxes the drug (Venlafaxine hydrochloride) was added in small quantities with continuous stirring until the drug was homogeneously dispersed in to the molten wax. The diluents were then added with continuous stirring in small quantities. When the molten wax cools to a temperature of 45^{O}c, it was passed through sieve No. 20. The solidified granules were collected and mixed with lubricants in a polyethylene bag for 15 minutes and then the granules were compressed on an 8 mm tablet punching machine.

Partial Melt Granulation

Hydrogenated castor oil flakes were first melted at 80-90^{O}c and then carnauba wax was added. To the molten mass the drug was gradually added in small quantities with continuous stirring. When molten mass was cooled to 45^{O}c, the mass was passed through sieve No.20 and solidified wax granules were collected. The solidified wax granules were mixed properly with diluents in a polyethylene bag for 15 minutes. The lubricants were then added to this mixture and mixed for another five minutes. The mixture was then compressed in an 8 mm tablet punches (clit pilot press).

Wet Granulation

Hydrogenated castor oil wax flakes and carnauba wax flakes were powdered and passed through 100 sieve. The powdered waxes, drug and diluents were mixed continuously in a polyethylene bag for 15 minutes. The mixture was transferred to a mortar and was triturated for 5 minutes and water was added in small quantities to mixture with continuous mixing. The wet mass was passed through sieve No. 20 to form granules. The wet granules were heated at 45^{o} in a hot air oven for 24 hours. The dried granules were then mixed with lubricants for 10 minutes in a polyethylene bag and then compressed (clit pilot press).

Direct Compression

Hydrogenated castor oil wax flakes and carnauba wax flaxes were powdered and passed through 100 sieve. The powdered waxes, drug and diluents were mixed together in a polyethylene bag for 15 minutes. The lubricants were then added and again mixed for 10 minutes and finally mixture was compressed (clit pilot press).

Evaluation of Physical Parameters of Wax Granules [14,15,17,8]

Flow Properties

Bulk density: Bulk density of granules was calculated by pouring gently 25 gms of sample through a glass funnel into a 50 ml graduated cylinder. The volume occupied by the sample was recorded.

Tapped Density: The measuring cylinder (50ml) containing 25 gm of sample was tapped with a fixed drop of 14 $\pm$ 2mm at a nominal rate of 300 drops per minute. The cylinder was tapped 500 times initially and the tapped volume was recorded and the tapped density was calculated.

Compressibility Index: It is a simple method which indicates the ease with which a material can be induced to flow. Thus flow properties can be determined.

Carr's Index: This is the simple test to evaluate the flow ability of a powder by comparing poured and tapped density of granules.

$$\text{Carr's Index (\%)} = \frac{\textit{Tapped density} - \textit{poured density}}{\textit{Tapped denisity}}$$

Hausner Ratio: This is the similar method which determines the flow property of granules.

$$\textit{Hausner Ratio} = \frac{\textit{Tapped denisity}}{\textit{Poured denisity}}$$

Angle of Repose

Flow properties of wax granules were determined by calculation of angle of repose by fixed funnel method. A funnel of 10mm internal diameter was placed at a fixed height (H) of 2 cm above graph paper that is

placed on a horizontal surface. 15 grams of sample was poured carefully through the funnel until the apex of the conical pile just touches the tip of the funnel. The average radius (R) of three such conical piles was measured. The angle of repose was calculated by using the following formula.

Drug Content: Ten tablets from each batch were crushed to powder and a quantity of 250 mg of powder was weighted and was transferred to 100 ml of distilled water. The drug was extracted from the wax by stirring on magnetic stirrer for two hours. The solution was filtered through watmann filter paper No. 1 one ml of solution was diluted to 10 ml and the absorbance was noted at 273 nm. The drug content was determined from calibration curve.[12,13]

***In-vitro* drug release studies**:[11] *In-vitro* drug release was determined by USP apparatus II. Dissolution studies for wax matrix tablets were conducted in triplicate.

Dissolution testing of wax matrix tablets was conducted under following conditions.

- USP dissolution apparatus: Type - II (paddle method)
- Speed of paddle rotation: 100 rpm
- Volume of dissolution: 900 ml
- Dissolution medium: Distilled water
- Number of samples: 3

Formulation parameters

Total wax concentration

Formulations from F_1 to F_{14} were prepared with different concentrations of wax by melt granulation technique. The composition of the formulation is shown in the table with different concentrations of wax in percentage. The effect of total wax on in vitro drug release was determined.[19]

Comparison with marketed preparations

The drug release profile of optimized batch was compared with three different marketed preparations Vexor(Cadila), Venla(Solus), Venlor(cipla), were studied.

Heat treatment of Wax Matrix Tablets

The tablets prepared by four methods i.e. Melt granulation, partial Melt granulation, wet granulation, Dry granulation were placed in a hot air oven (Spectrum Pvt. Limited) which is maintained at 80°. After 30 minutes, the tablets were removed from oven and they were allowed to cool to room temperature. Dissolution tests were done and drug release profile of all tablets was determined after 24 hours.[15,18]

Composition in percentage

	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}	F_{11}	F_{12}	F_{13}	F_{14}
CW	20	25	30	35	5	10	15	20	25	25	25	15	40	-
HCO	5	5	5	5	20	20	20	20	5	10	15	25	-	40
VNHcl	15	15	15	15	15	15	15	15	15	15	15	15	15	15
DCPD	43	43	43	43	43	43	43	43	43	43	43	43	43	43
Mgs	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1	1	1	1	1	1

Results and Discussion

Flow properties of Granules

The granules prepared by passing through 20 sieve i.e. with size 850 µm by four different methods were analyzed for different parameters. Bulk density, tapped density, angle of repose, compressibility index, Hausner ratio for four different methods are given in the table below.

Physical evaluation of wax granules (mean±S.D.)

Methods	Bulk Density	Tapped Density	Compressibility Index	Hausner Ratio	Angle of respose (θ)
MG	0.7413± 0.0016	0.7616±0.0012	2.66± 0.0076	1.05±0.024	27.66±0.204
PMG	0.7136±0.003	0.7556±0.0041	5.09±0.024	1.058±0.036	28.486±0.2877
WG	0.7692±0.008	0.8890±0.004	13.47±0.42	1.156±0.022	31.46±0.310
DC	0.8990± 0.0014	0.6870±0.0012	23.58±0.028	1.294± 0.96	48.78± 0.264

MG = Melt granulation PMG = Partial melt granulation

DC = Direct Compression WG = Wet granulation

Evaluation of Various physical parameters of Venlafaxine Hydrochloride wax matrix tablets.

Appearance: The appearance of tablets was done by visual examination. The tablets were circular or round and the colour of tablets was light brown. The color was due to carnauba wax.

The thickness, weight variation, Hardness and friability of tablet are shown in table below:

Evaluation of physical parameters of Venlafaxine Hydrochloride wax matrix tablets (mean±SD)

Batch	Weight variation (n=20)	Thickness (n=3)	Hardness (n=3)	Drug Content (n=10)	Friability (n=6)
F_1	254±2.50	4.41±0.18	4.6±0.081	98.86±0.15	0.12
F_2	249±1.76	4.76±0.176	4.4±0.081	98.47±0.22	0.20
F_3	251±1.58	4.58±0.039	4.3±0.169	98.22±0.102	0.31
F_4	247±3.50	4.70±0.036	4.5±0.124	98.046±0.908	0.42
F_5	248±3.45	4.81±0.049	4.6±0.124	98.33±1.05	0.12
F_6	249±2.10	5.06±0.020	4.36±0.124	98.08±0.375	0.14
F_7	250±4.12	4.37±0.053	4.3±0.163	98.49±1.79	0.21
F_8	251±3.25	4.32±0.042	4.3±0.163	97.14±1.78	0.36
F_9	250±4.15	4.40±0.062	4.2±0.081	97.51±1.22	0.26
F_{10}	252±3.60	4.38±0.041	4.4±0.081	99.52±0.22	0.22
F_{11}	248±5.25	4.66±0.022	4.7±0.081	99.31±0.089	0.28
F_{12}	249±4.10	4.32±0.018	4.63±0.124	99.36±0.218	0.31
F_{13}	251±3.55	4.41±0.019	4.8±0.081	99.09±0.081	0.16
F_{14}	250±4.52	4.40±0.021	4.1±0.124	97.69±0.081	0.18
F_{15}	250±5.03	4.48±0.022	4.2±0.081	98.28±0.375	0.11
F_{16}	250±5.02	4.37±0.024	4.5±0.124	98.056±0.806	0.14

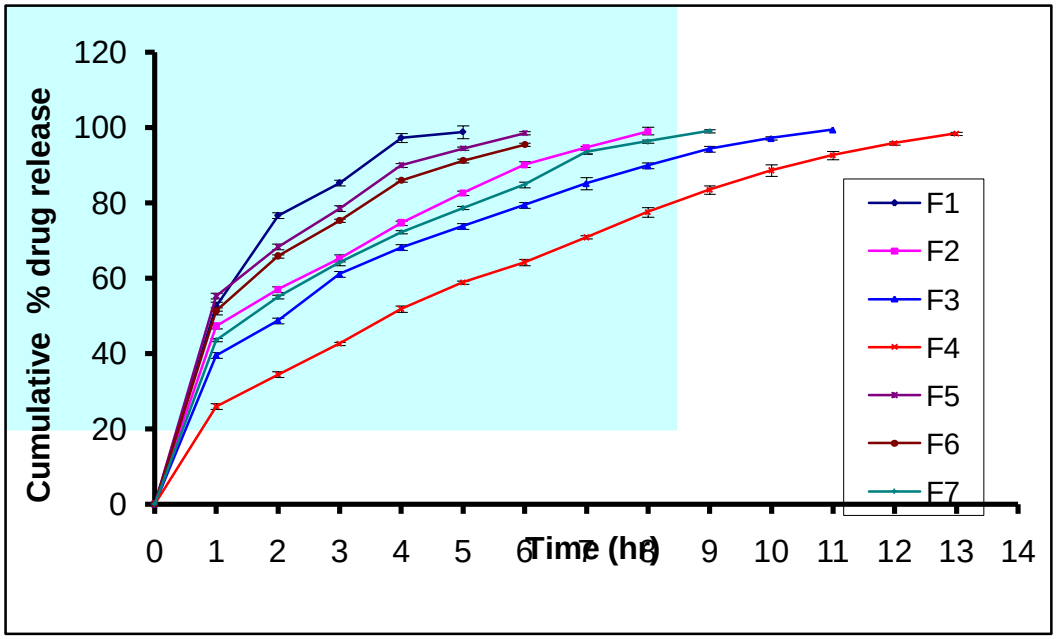
Effect of Formulation parameters on drug release

Effect of Total Wax

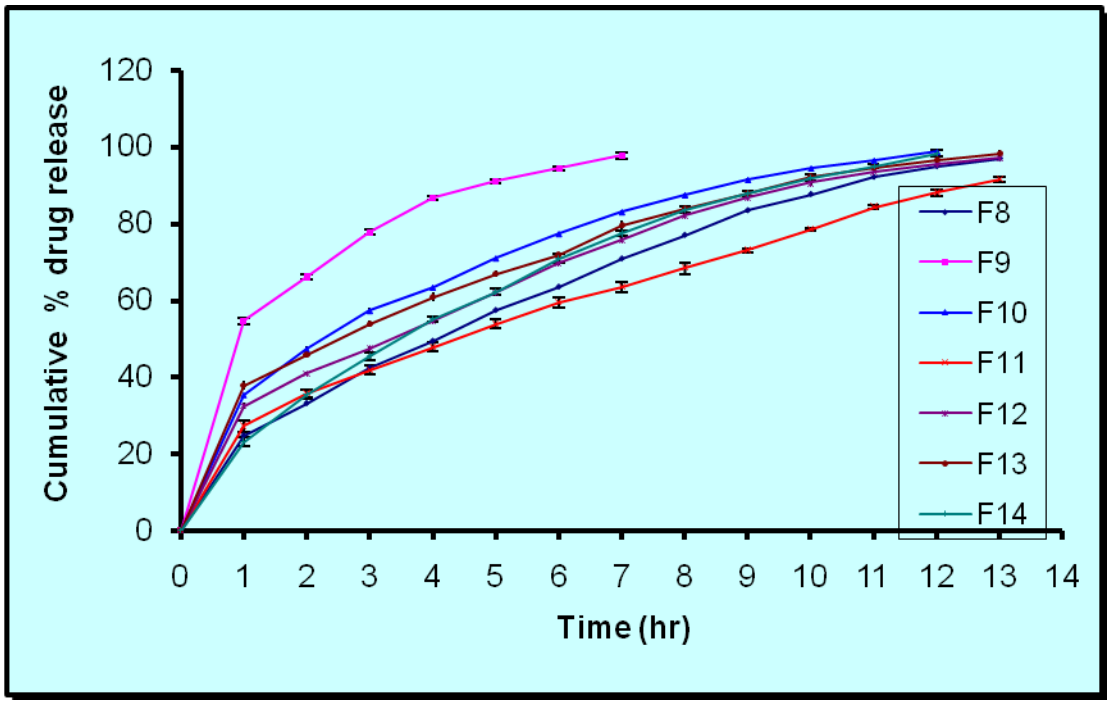
Effect of wax concentration on drug release (mean±SD)

S/No	Time	F_1	F_2	F_3	F_4	F_5	F_6	F_7
1	1	52.522±1.15	47.272±0.87	39.508±0.75	25.983±0.75	55.287±0.75	51.279±0.93	43.515±0.43
2.	2	76.612±0.75	57.052±0.75	48.744±0.76	34.392±0.75	68.367±0.75	65.841±0.43	55.028±0.44
3.	3	85.290±0.75	65.132±1.15	61.036±0.76	42.597±0.43	78.514±0.75	75.221±0.44	64.098±0.76
4.	4	97.227±1.14	74.758±0.44	68.134±0.76	51.849±0.87	89.966±0.44	85.905±0.43	72.216±0.44
5.	5	98.792±1.74	82.682±0.44	73.768±0.76	58.896±0.44	94.432±0.44	91.135±0.44	78.623±0.44
6.	6		90.147±0.75	79.431±0.77	64.228±0.87	98.475±0.44	95.390±0.43	84.813±0.76
7.	7		94.645±0.45	85.123±0.77	70.840±0.45			93.528±0.45
8.	8		98.915±1.16	89.842±1.59	77.486±1.32			96.285±0.46
9.	9			94.355±0.78	83.416±1.16			99.056±0.46
10.	10			97.097±0.76	88.626±1.58			
11.	11			99.370±0.43	92.609±1.17			
12.	12				95.860±0.04			
13.	13				98.376±0.42			

S/No	Time	F_8	F_9	F_{10}	F_{11}	F_{12}	F_{13}	F_{14}
1	1	24.7300±0.43	54.535±0.75	35.250±0.43	27.235±1.56	32.45±0.75	37.754±1.15	23.228±1.15
2.	2	33.133±0.44	66.109±0.75	47.217±0.75	35.652±1.15	40.942±0.43	45.728±0.76	35.379±1.14
3.	3	42.333±0.45	77.746±0.76	57.247±0.76	41.860±1.14	47.430±0.75	53.996±0.88	45.343±1.15
4.	4	49.329±0.44	86.689±0.44	63.323±0.43	47.851±1.16	54.704±0.43	60.806±1.16	55.110±0.76
5.	5	57.364±0.45	90.922±0.44	70.934±0.43	53.874±1.31	62.017±0.44	66.900±0.76	62.176±0.77
6.	6	63.439±0.44	94.424±0.44	77.333±0.43	59.429±1.32	69.620±0.43	71.774±0.77	70.782±1.15
7.	7	70.798±0.44	97.692±0.76	83.014±0.44	63.509±1.33	75.760±0.75	79.728±1.14	77.430±0.77
8.	8	76.944±0.44		87.471±0.43	68.363±1.53	82.182±0.75	83.866±0.78	83.612±0.77
9.	9	83.372±0.45		91.451±0.43	72.990±0.47	86.885±0.44	88.076±0.76	87.822±0.78
10.	10	87.579±0.45		94.447±0.43	78.393±0.39	90.610±0.76	92.307±0.76	92.053±0.78
11.	11	92.058±0.45		96.456±0.43	84.324±0.41	93.601±0.42	94.806±0.46	95.052±0.45
12.	12	94.806±0.44		98.724±0.75	88.032±0.75	95.604±0.43	96.565±0.47	98.316±0.78
13.	13	96.815±0.44			91.508±0.75	97.115±0.43	98.330±0.79	



Effect of concentration of wax on drug release (F_1 to F_7)



Effect of concentration of wax on drug release (F_8 to F_{14})

Tablets were prepared by melt granulation technique with varying concentration of two waxes

Formulations from F_1 to F_{14} contained different concentrations of wax. Formulations from F_1 to F_{12} contained combination of two waxes i.e. Hydrogenated castor oil and carnauba wax.Formulation (F_{11}) gave the highest release of the drug and it was the optimized formulation. F_{11} is the formulation with 25% carnauba wax and 15% hydrogenated castor oil. Highest release was obtained because carnauba wax sustains the drug release and Hydrogenated castor oil coats the granule and further sustains drug release. F_{12} has same total wax concentration but drug release is decreased because concentration of carnauba wax is less than hydrogenated castor oil. The carnauba wax maybe better retarding agent than Hydrogenated castor oil. F13 (13 hrs) and F14 (12 hrs) contain only one wax in their composition and the release showed by them is lesser than the earlier formulations. This suggests that combination of two waxes increases the sustaining effect on drug release.

As the wax concentration is increased the sustaining effect of drug is also increased, this may be due to increased distance that a drug should travel due to increased porosity and tortuosity.

27.235% was the initial release of drug from wax matrix.

Heat treatment of tablets drastically decreased the drug release from the wax matrix tablets in order of MG, PMG, DC and WG respectively. Comparison of drug release profiles before heat treatment and after treatment showed a drastic change i.e., decrease in drug release from the tablets prepared by four methods. Heat treatment of the tablets caused the wax to melt and redistribute. After cooling to room temperature, the wax resolidifies and forms a new matrix. The analysis of the dissolution data revealed that the tortuosity of the matrix increased after heat treatment. Therefore heat treatment caused the distribution of the wax and formed a new matrix system with higher tortuosity, resulting in decrease of drug release.

Heat treatment of Wax Matrix Tablets

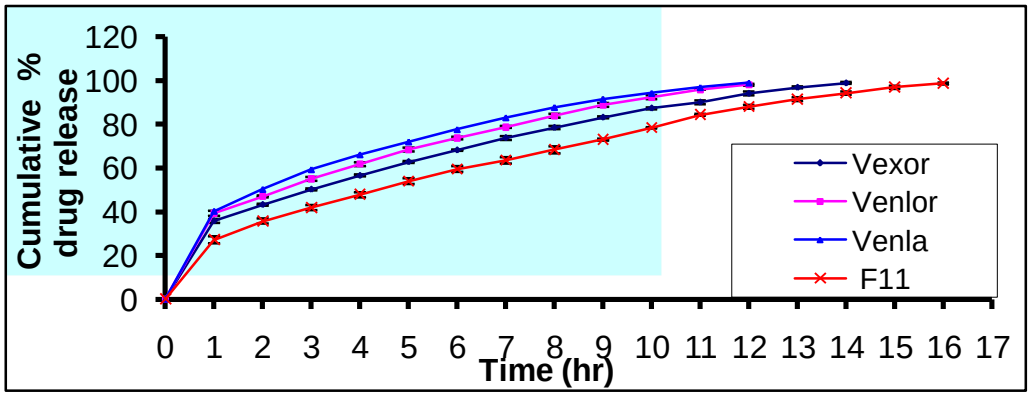
Effect of heat treatment of wax matrix tablets on drug release

S.No.	Time(hr)	Cumulative % drug release (mean ± SD)			
		MG	PMG	DC	WG
1.	1	9.652 ± 0.11	16.465 ± 1.15	39.508 ± 0.75	42.012 ± 1.15
2.	2	14.081 ± 0.08	22.067 ± 0.87	47.992 ± 0.76	54.017 ± 0.75
3.	3	19.233± 0.08	29.953 ± 1.29	55.020 ± 0.76	62.581± 0.75
4.	4	25.291 ± 0.16	37.131 ± 0.86	62.336± 0.43	70.190 ±0.44
5.	5	31.166 ± 1.02	43.597 ± 1.15	68.439 ± 0.01	76.836 ± 0.76
6.	6	38.072 ± 1.50	49.346 ± 0.76	74.072± 0.76	83.017 ± 0.43
7.	7	45.543 ± 1.53	54.875 ± 0.76	79.234 ± 1.16	88.227 ± 0.76
8.	8	51.300± 0.77	59.683 ± 0.77	84.673 ± 0.43	91.962 ± 0.45
9.	9	58.090 ± 0.45	64.515 ± 0.77	93.625 ± 0.45	95.464± 0.45
10.	10	63.915 ± 0.77	69.652 ± 0.75	96.632 ± 0.77	98.231 ± 0.45
11.	11	65.512 ± 0.76	75.758 ± 0.46	98.400 ± 0.43	
12.	12	68.917 ± 0.75	79.167± 0.78		
13.	13	71.861 ± 0.44	84.099 ± 0.79		
14.	14	75.451 ± 0.77	88.055 ± 1.19		
15.	15	79.551 ± 0.45	91.279± 0.91		
16.	16	81.265 ± 0.44	94.017 ± 1.20		

Comparison with marketed preparations

The optimized batch was compared with the following marketed preparation, vexor (cadila), venlor (cipla), venla (solus). Vexor (cadila) gave the drug release for 14 hours and venla and venlor gave drug release for 12 hours. The drug release of optimized batch is higher than that of above three marketed preparations.

S/No.	Time (hr)	Cumulative % drug release (mean ± SD)			
		Vexor	Venlor	Venla	F_{11} (Optimized batch)
1.	1	35.751 ± 0.75	39.257 ± 1.25	40.235 ± 0.43	27.235 ± 1.56
2.	2	43.213 ± 0.43	46.989 ± 0.43	50.249 ± 0.75	35.652 ±1.15
3.	3	50.214± 0.44	55.013± 0.76	59.293 ± 0.43	41.860 ± 1.14
4.	4	56.502 ± 0.44	61.826 ± 0.88	66.133 ± 0.44	47.851 ± 1.16
5.	5	62.823 ± 0.44	68.429 ± 0.77	72.006 ± 0.87	53.874± 1.31
6.	6	68.175 ± 0.42	73.722 ± 0.45	77.660 ± 0.44	59.429 ±1.32
7.	7	73.806 ± 0.87	78.722 ± 0.45	83.091 ± 0.43	63.509 ± 1.33
8.	8	78.465± 0.76	83.908 ± 0.77	87.800± 0.76	68.363 ± 1.53
9.	9	83.146 ± 0.45	88.868 ± 0.77	91.530± 1.16	72.990 ± 0.47
10.	10	87.351 ± 0.45	92.353 ± 0.78	94.276 ± 0.45	78.393 ±0.41
11.	11	90.043 ± 0.89	95.854 ± 0.03	96.920± 0.02	84.324 ± 0.41
12.	12	94.043 ± 0.89	98.119 ± 0.46	99.012±0.44	88.032± 0.75
13.	13	96.817 ± 0.44			91.508 ± 0.75
14.	14	98.833 ± 0.45			94.248 ± 0.75
15.	15				97.002± 0.76
16.	16				98.766± 0.42



Comparison of release profile of F_{11} with marketed preparations

Conclusion

In the present investigation, sustained release matrix tablet was prepared using the combination of carnauba wax and hydrogenated castor oil. Venlafaxine Hydrochloride, a unique antidepressant which structurally differs from other novel antidepressants, was used as model drug. It is a highly water soluble and highly permeable drug with elimination half life of 5±2 hours and pKa of 9.4. Waxes were used in this study as binding agents. Waxes are biodegradable, biocompatible, ecofriendly, cost effective and have good stability at varying P^H and humidity. Carnauba wax and Hydrogenated castor oil, which are high melting point waxes, were used as binding agents in this investigation.

Melt granulation was used as method of preparation. It is advantageous compared with an ordinary wet granulation process, since the liquid addition phase as well as drying phase of the process is eliminated. Melt granulation needs less heat energy and no solvents are required and water sensitive materials can be used in this method. Fourteen formulations from (F_1 to F_{14}) were prepared with different composition of waxes. F_{11} was the optimized formulation which gave a 16 hours release of drug (98%).Formulation (F_{11}) has 40% w/w of total wax. Formulation F_{12} also had 40% w/w of wax but gave a drug release of 14 hours because of less concentration of carnauba wax. Formulation (F_8) also gave a sustained release of 14 hours. This indicates that correct proportion of carnauba wax and Hydrogenated castor oil is 25% w/w and 15% w/w respectively.

Various formulation parameters were studied to determine their effect of drug release. The Dicalcium phosphate dihydrate was replaced by starch, Microcrystalline cellulose, lactose. Tablets with starch and microcrystalline cellulose gave burst release and lactose gave faster release of drug. Various process variables were studied to determine their effect of drug release. Drug release increased in the order of Melt granulation, Partial melt granulation, direct compression and wet granulation. Direct compression and Wet granulation gave burst release. With increase in dispersion time up to 20 minutes the drug release was decreased and for 30 minutes, drug release may have increased because of redispersion. Heat treatment of tablets showed decrease in in-vitro drug release. The tablets were intact and smooth Thus it can be concluded that sustained release wax matrix tablets were prepared successfully using the combination of carnauba wax and Hydrogenated castor oil for a highly water soluble drug, Venlafaxine Hydrochloride.

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How to cite this article

Sarode S., Patil P.R, Md. Rageeb Md. Usman, Vadnere G.P. and Sagar G.V. (2014). Preparation and Characterization of Sustained release Antidepressant tablet using combination of wax., *Int. J. Pharm. Life Sci.*, 5(8):3787-3798.

Source of Support: Nil; Conflict of Interest: None declared

Received: 15.07.14; Revised: 03.08.14; Accepted:10.08.14